ordered ref 1

```
> s ovarian cancer

         68566 OVARIAN
        314596 CANCER
L1        9941 OVARIAN CANCER
               (OVARIAN(W)CANCER)

=> s pi kinase

         30449 PI
        129484 KINASE
L2        136 PI KINASE
               (PI(W)KINASE)

=> s l1 and l2

L3            0 L1 AND L2

=> s pik3ca

L4            6 PIK3CA

=> s l1 and l4

L5            3 L1 AND L4

=> d l5 1-3 bib,ab


L5   ANSWER 1 OF 3  MEDLINE
AN   2000090217     MEDLINE
DN   20090217
TI   Growth suppression of human ovarian cancer cells by
     adenovirus-mediated transfer of the PTEN gene.
AU   Minaguchi T; Mori T; Kanamori Y; Matsushima M; Yoshikawa H; Taketani Y;
     Nakamura Y
CS   Laboratory of Molecular Medicine, Human Genome Center, The Institute of
     Medical Science, The University of Tokyo, Japan.
SO   CANCER RESEARCH, (1999 Dec 15) 59 (24) 6063-7.
     Journal code: CNF. ISSN: 0008-5472.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals; Cancer Journals
EM   200003
EW   20000305
AB   A tumor suppressor gene on chromosome 10q23, PTEN, encodes a
     phosphatidylinositol phosphatase that antagonizes activation of the
     phosphatidylinositol 3'-kinase-mediated pathway involved in cell growth.
A
     gene encoding the catalytic subunit of phosphatidylinositol 3'-kinase (
     PIK3CA) is frequently activated in ovarian cancers; therefore,
     overexpression of the PTEN product through gene transfer might be an
     effective strategy for treating ovarian cancers. To test the potential
for
     this type of gene therapy, we constructed a recombinant adenovirus
     encoding wild-type PTEN and examined its effects on nine cell lines
     derived from human ovarian carcinomas. Transduction of the PTEN gene
     significantly inhibited growth of six of these cell lines compared with
```

infection with virus alone, and the degree of inhibition correlated with the efficiency of gene transfer as determined by beta-galactosidase assay.

Results of flow cytometry suggested that the observed effects were mediated by two mechanisms, apoptosis and/or arrest in the G1 phase of the cell cycle, and that high adenoviral transduction efficiency of cells was associated with induction of apoptosis. We also found that the level of transcription of Integrin alpha(v) in **ovarian cancer** cells correlated with the efficiency of transduction (P = 0.014) and with the degree of growth inhibition after PTEN gene transfer (P = 0.009). These findings carry significant implications for adenovirus vector-based PTEN gene therapies for ovarian cancers.

L5 ANSWER 2 OF 3 MEDLINE
AN 2000025001 MEDLINE
DN 20025001
TI **PIK3CA**: determining its role in cellular proliferation and **ovarian cancer**.
AU Andrew S
CS Department of Medical Genetics, University of Alberta, Edmonton, Canada.. seandrew@pop.srv.ualberta.ca
SO CLINICAL GENETICS, (1999 Sep) 56 (3) 190-1.
Journal code: DDT. ISSN: 0009-9163.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200001
EW 20000104

L5 ANSWER 3 OF 3 MEDLINE
AN 1999113837 MEDLINE
DN 99113837
TI **PIK3CA** is implicated as an oncogene in **ovarian cancer** [see comments].
CM Comment in: Nat Genet 1999 Jan;21(1):64-5
AU Shayesteh L; Lu Y; Kuo W L; Baldocchi R; Godfrey T; Collins C; Pinkel D; Powell B; Mills G B; Gray J W
CS UCSF Cancer Center, University of California, San Francisco 941430-0808, USA.
NC CA09215 (NCI)
P01-CA64602 (NCI)
SO NATURE GENETICS, (1999 Jan) 21 (1) 99-102.
Journal code: BRO. ISSN: 1061-4036.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199904
EW 19990402
AB **Ovarian cancer** is the leading cause of death from gynecological malignancy and the fourth leading cause of cancer death among American women, yet little is known about its molecular aetiology. Studies using comparative genomic hybridization (CGH) have revealed several regions of recurrent, abnormal, DNA sequence copy number that may encode genes involved in the genesis or progression of the disease. One region at 3q26 found to be increased in copy number in approximately 40% of ovarian and others cancers contains **PIK3CA**, which encodes the p110alpha catalytic subunit of phosphatidylinositol 3-kinase (PI3-kinase).

The association between **PIK3CA** copy number and PI3-kinase activity makes **PIK3CA** a candidate oncogene because a broad range of cancer-related functions have been associated with PI3-kinase mediated signalling. These include proliferation, glucose transport and catabolism,

cell adhesion, apoptosis, RAS signalling and oncogenic transformation. In addition, downstream effectors of PI3-kinase, AKT1 and AKT2, have been found to be amplified or activated in human tumours, including **ovarian cancer**. We show here that **PIK3CA** is frequently increased in copy number in ovarian cancers, that the increased copy number is associated with increased **PIK3CA** transcription, p110alpha protein expression and PI3-kinase activity and that treatment with the PI3-kinase inhibitor LY294002 decreases proliferation and increases apoptosis. Our observations suggest **PIK3CA** is an oncogene that has an important role in **ovarian cancer**.

N 2000090217 MEDLINE
DN 20090217
TI Growth suppression of human **ovarian cancer** cells by adenovirus-mediated transfer of the PTEN gene.
AU Minaguchi T; Mori T; Kanamori Y; Matsushima M; Yoshikawa H; Taketani Y; Nakamura Y
CS Laboratory of Molecular Medicine, Human Genome Center, The Institute of Medical Science, The University of Tokyo, Japan.
SO CANCER RESEARCH, (1999 Dec 15) 59 (24) 6063-7.
Journal code: CNF. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 200003
EW 20000305
AB A tumor suppressor gene on chromosome 10q23, PTEN, encodes a phosphatidylinositol phosphatase that antagonizes activation of the **phosphatidylinositol** 3'-**kinase**-mediated pathway involved in cell growth. A gene encoding the catalytic subunit of **phosphatidylinositol** 3'-**kinase** (PIK3CA) is frequently activated in ovarian cancers; therefore, overexpression of the PTEN product through gene transfer might be an effective strategy for treating ovarian cancers. To test the potential for this type of gene therapy, we constructed a recombinant adenovirus encoding wild-type PTEN and examined its effects on nine cell lines derived from human ovarian carcinomas. Transduction of the PTEN gene significantly inhibited growth of six of these cell lines compared with infection with virus alone, and the degree of inhibition correlated with the efficiency of gene transfer as determined by beta-galactosidase assay. Results of flow cytometry suggested that the observed effects were mediated by two mechanisms, apoptosis and/or arrest in the G1 phase of the cell cycle, and that high adenoviral transduction efficiency of cells was associated with induction of apoptosis. We also found that the level of transcription of Integrin alpha(v) in **ovarian cancer** cells correlated with the efficiency of transduction (P = 0.014) and with the degree of growth inhibition after PTEN gene transfer (P = 0.009). These findings carry significant implications for adenovirus vector-based PTEN gene therapies for ovarian cancers.

L7 ANSWER 2 OF 7 MEDLINE
AN 2000025001 MEDLINE
DN 20025001
TI PIK3CA: determining its role in cellular proliferation and **ovarian cancer**.
AU Andrew S
CS Department of Medical Genetics, University of Alberta, Edmonton, Canada.. seandrew@pop.srv.ualberta.ca
SO CLINICAL GENETICS, (1999 Sep) 56 (3) 190-1.
Journal code: DDT. ISSN: 0009-9163.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200001
EW 20000104

L7 ANSWER 3 OF 7 MEDLINE
AN 1999184222 MEDLINE

DN 99184222
TI **Ovarian cancer** investigators aim at cell signaling pathways [news].
AU Friedrich M J
SO JAMA, (1999 Mar 17) 281 (11) 973-5.
Journal code: KFR. ISSN: 0098-7484.
CY United States
DT News Announcement
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199905
EW 19990504

L7 ANSWER 4 OF 7 MEDLINE
AN 1999113837 MEDLINE
DN 99113837
TI PIK3CA is implicated as an oncogene in **ovarian cancer** [see comments].
CM Comment in: Nat Genet 1999 Jan;21(1):64-5
AU Shayesteh L; Lu Y; Kuo W L; Baldocchi R; Godfrey T; Collins C; Pinkel D; Powell B; Mills G B; Gray J W
CS UCSF Cancer Center, University of California, San Francisco 941430-0808, USA.
NC CA09215 (NCI)
P01-CA64602 (NCI)
SO NATURE GENETICS, (1999 Jan) 21 (1) 99-102.
Journal code: BRO. ISSN: 1061-4036.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199904
EW 19990402
AB **Ovarian cancer** is the leading cause of death from gynecological malignancy and the fourth leading cause of cancer death among American women, yet little is known about its molecular aetiology. Studies using comparative genomic hybridization (CGH) have revealed several regions of recurrent, abnormal, DNA sequence copy number that may encode genes involved in the genesis or progression of the disease. One region at 3q26 found to be increased in copy number in approximately 40% of ovarian and others cancers contains PIK3CA, which encodes the p110alpha catalytic subunit of **phosphatidylinositol** 3-**kinase** (PI3-kinase). The association between PIK3CA copy number and PI3-kinase activity makes PIK3CA a candidate oncogene because a broad range of cancer-related functions have been associated with PI3-kinase mediated signalling. These include proliferation, glucose transport and catabolism, cell adhesion, apoptosis, RAS signalling and oncogenic transformation. In addition, downstream effectors of PI3-kinase, AKT1 and AKT2, have been found to be amplified or activated in human tumours, including **ovarian cancer**. We show here that PIK3CA is frequently increased in copy number in ovarian cancers, that the increased copy number is associated with increased PIK3CA transcription, p110alpha protein expression and PI3-kinase activity and that treatment with the PI3-kinase inhibitor LY294002 decreases proliferation and increases apoptosis. Our observations suggest PIK3CA is an oncogene that has an important role in **ovarian cancer**.

L7 ANSWER 5 OF 7 MEDLINE
AN 97159701 MEDLINE
DN 97159701
TI HER-2/neu signal transduction in human breast and **ovarian cancer**.
AU Reese D M; Slamon D J

CS Division of Hematology/Oncology and Jonsson Comprehensive Cancer Center, UCLA School of Medicine, Los Angeles, California 90[redacted]5, USA.
NC 1K12CA01714 (NCI)
R01 CA36827 (NCI)
SO STEM CELLS, (1997) 15 (1) 1-8. Ref: 85
Journal code: BN2. ISSN: 1066-5099.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199707
AB The HER-2/neu proto-oncogene encodes a 185 kDa transmembrane receptor tyrosine kinase with significant sequence homology to other members of the class I receptor tyrosine kinase family. The HER-2/neu gene is amplified and/or overexpressed in 25%-30% of human breast and ovarian cancers, and overexpression of the receptor is associated with poor prognosis. Tyrosine phosphorylation and activation of the HER-2 receptor lead to activation of specific signal transduction pathways in breast and **ovarian cancer** cells, including the ras/MAP **kinase** cascade, **phosphatidylinositol** 3-**kinase**, and phospholipase C-gamma. HER-2/neu signal transduction pathways ultimately converge on the cell nucleus, where the expression of diverse genes is induced after activation of the receptor. A more complete understanding of HER-2/neu signal transduction pathways may allow the development of specific therapeutics for the treatment of those human breast and ovarian cancers containing this alteration.

L7 ANSWER 6 OF 7 MEDLINE
AN 96150936 MEDLINE
DN 96150936
TI SH2 and SH3 domains: potential targets for anti-cancer drug design.
AU Smithgall T E
CS Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha 68198-6805, USA.
SO JOURNAL OF PHARMACOLOGICAL AND TOXICOLOGICAL METHODS, (1995 Nov) 34 (3) 125-32. Ref: 52
Journal code: A9W. ISSN: 1056-8719.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199605
AB Protein-tyrosine kinases interact with a diverse group of signaling molecules that share common structural elements known as Src homology 2 and 3 (SH2 and SH3) domains. SH2 domains bind with high affinity to peptide sequences within target proteins that contain phosphorylated tyrosine residues, but have no affinity for the unphosphorylated sequence. This property allows activated tyrosine kinases to initiate signal transduction by recruiting downstream effectors with SH2 domains. SH3 domains also mediate protein-protein interaction. Target sequences for SH3 domains are rich in proline and hydrophobic amino acids, but do not require phosphorylation. SH2- and SH3-mediated protein-protein interactions are required for the transmission of proliferative signals initiated by tyrosine kinases (e.g., Ras activation or stimulation of **phosphatidylinositol**-3' **kinase** activity). Peptidomimetic

ligands based on the sequence of target proteins for SH2 and SH3 domains may represent new lead compounds for the therapy of proliferative diseases that are dependent upon constitutively activated tyrosine kinases (e.g., BCR/ABL in chronic myelogenous and acute lymphocytic leukemias or HER-2/Neu in breast and **ovarian cancer**.

L7 ANSWER 7 OF 7 MEDLINE
AN 95309792 MEDLINE
DN 95309792
TI Evidence for tight coupling of gonadotropin-releasing hormone receptors to **phosphatidylinositol kinase** in plasma membrane from ovarian carcinomas.
AU Takagi H; Imai A; Furui T; Horibe S; Fuseya T; Tamaya T
CS Department of Obstetrics and Gynecology, Gifu University School of Medicine, Japan.
SO GYNECOLOGIC ONCOLOGY, (1995 Jul) 58 (1) 110-5.
Journal code: FXC. ISSN: 0090-8258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199509
AB Gonadotropin-releasing hormone (Gn-RH) analogs inhibit **ovarian cancer** cell proliferation in vivo and in vitro. To examine whether Gn-RH receptor (Gn-RHR) mediates direct antiproliferative effects, we attempted to determine inhibitory regulation by Gn-RH of **phosphatidylinositol** (PtdIns) **kinase** activity, known to stimulate mitogenic response, in plasma membranes isolated from ovarian carcinoma samples. Ovarian carcinomas surgically removed and cloned cell line SK-OV3 had been screened for Gn-RHR expression prior to plasma membrane isolation. PtdIns kinase activity was measured as phosphorylation of exogenous substrate PtdIns by the purified plasma membranes. Incubation of the plasma membranes isolated from Gn-RHR-positive specimens with [gamma-32P]ATP and PtdIns caused [32P]phosphate incorporation into PtdIns phosphate (PtdInsP) in a time-dependent manner. Concomitant exposure of the membrane preparations to Gn-RH analog buserelin (1 microM) led to a 70% inhibition of the PtdInsP production, when compared to control. After 10 or 15 min of an initial incubation, the addition of analog resulted in similar suppression of PtdIns phosphorylation. This inhibition was dependent on the buserelin dose, and a half-maximal effect occurred at a concentration 0.1 to 1 nM of buserelin. Degradation of the produced PtdInsP in the plasma membranes was not affected by the Gn-RH analog. Similar inhibition of PtdIns kinase activities was observed in membranes prepared from cells that had been pretreated with buserelin (1 microM) for 48 hr prior to assay. These findings demonstrate that PtdIns kinase activity is suppressed by Gn-RH analog in plasma membrane isolated from GnRHR-expressing ovarian carcinomas, suggesting a tight coupling of Gn-RHR to PtdIns. The inhibition of membrane-associated PtdIns kinase by Gn-RHR occupancy may mediate the antimitogenic action of the hormone on human ovarian carcinomas.

8 ANSWER 3 OF 4 MEDLINE
AN 1999422308 MEDLINE
DN 99422308
TI Expression analysis of genes at 3q26-q27 involved in frequent amplification in squamous cell lung carcinoma.
AU Racz A; Brass N; Heckel D; Pahl S; Remberger K; Meese E
CS Department of Human Genetics, Medical School, University of Saarland, Homburg/Saar, Germany.
SO EUROPEAN JOURNAL OF CANCER, (1999 Apr) 35 (4) 641-6.
Journal code: ARV. ISSN: 0959-8049.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199912
EW 19991202
AB Gene amplifications are known to occur frequently in lung **cancer** . Recently, we identified gene amplifications at 3q26 in squamous cell lung carcinoma (SCC) using reverse chromosome painting. Here, our aim was to analyse the expression of genes which map within the amplified chromosomal region. The genes which were selected for their known function and their potential involvement in tumour development included the genes for ribosomal protein L22 (RPL22), butyrylcholinesterase (BCHE), glucose transporter 2 (SLC2A2), transferrin receptor (TFRC), thrombopoietin (THPO) and the phosphatidylinositol-3 kinase catalytic alpha polypeptide (**PIK3CA**). While five genes were expressed in the majority of the 17 samples of SCC, the gene for the glucose transporter 2 (SLC2A2) was expressed in only three cases, excluding SLC2A2 as the target gene of the amplification unit. For a subset of tumours, we determined the amplification status of the six genes. The TFRC, **PIK3CA**, BCHE, THPO and SLC2A2 genes were amplified in several cases, whereas the RPL22 gene was amplified in only one case. The combined amplification and expression data of this and our previous studies indicate that the amplified region at 3q26 contains several genes that are transcribed in SCC, providing the possibility that several amplified and functionally important genes at 3q26 may be involved in the pathogenesis of SCC.